Recent developments in biologic therapies for the treatment of patients with systemic lupus erythematosus

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Abstract

SLE has a complex pathogenesis, and multiple therapeutic targets have been discovered in recent years. In spite of belimumab being approved by the US Food and Drug Administration and the widespread use of rituximab, there have been many failed attempts to treat SLE successfully using biologic agents. In this review, we consider newer biologic approaches that might offer the hope of improving the outcome of SLE patients. These include the fully humanized anti-CD20 mAbs, PEGylated anti-CD40L, IFN-γ inhibitors, rigerimod and immune complexes blockade.

Key words: lupus, biologic, anti-CD20, anti-CD40L, daiprolizumab, ofatumumab, obinutuzumab, rigerimod, interferon, FC\(_R\)

Rheumatology key messages

- There is still considerable morbidity with conventional immunosuppression in SLE patients.
- Successful biologic use in SLE is a decade behind that for rheumatoid and psoriatic arthritis.
- A number of new promising biologic therapies for SLE are in clinical trials.

Introduction

The use of biologic therapies in the treatment of patients with SLE is, arguably, at least a decade behind their use in RA, PsA and AS. The need for more successful biologic or other new therapies remains important as it is clear we have reached the limit of what can be achieved with conventional immunosuppression [1]. SLE patients have ~90% survival rate at 10 years [2] with considerable morbidity, which remains very unsatisfactory for a disease that often develops before age 30.

Some encouragement is taken from the approval of belimumab by the US Food and Drug Administration (and more recently the National Institute for Health and Clinical Excellence) and the widespread use of rituximab (in spite of two trials that did not meet their endpoints). Neither drug alone will be a panacea for SLE, although interestingly attempts to combine those drugs are now being pursued. In this mini-review we will focus on several new or modified approaches that we believe offer the best hope of improving the outcome of SLE patients. Our choice of new approaches is subjective, based on our reading of the recent literature.

Pathogenesis

The pathogenesis of SLE involves genetic and epigenetic factors, environmental triggers and immunological abnormalities. These abnormalities include defective apoptosis and loss of tolerance; inadequate development of dendritic cells; defective function of regulatory T cells and B cells; defective B and T cells apoptosis and defective signalling pathways. Fig. 1 shows the link between these factors and the sites of action of relevant therapeutic agents.

CD20 blockade

B cells play an essential role in the development of SLE. Blocking B cells with rituximab, a chimeric mAb against antigen CD20, is well established in SLE. Because it is a chimeric antibody, can cause allergic responses in ~10% of SLE patients. Fully humanized mAbs anti-CD20 have been developed including ofatumumab and obinutuzumab.
Defective apoptosis results in production of uncleared nuclear material leading to dendritic-cells (DC) activation and BCR stimulation. DC will produce a number of cytokines, which will result in B-cell activation (BAFF and APRIL) but also differentiation of monocytes to macrophages (IFNs) that will present self-antigens to T and B cells but also produce cytokines. The activation of B cells needs a co-stimulatory signal between T-cell receptor (TCR) and MHC in antigen presenting cells (APC) but also CD40: CD40L binding with macrophage and dendritic cells. B-cells activation, differentiation, and proliferation leads to autoantibody production. Immune complex formation and tissue deposition results in organ damage. pDC: plasmacytoid dendritic cells; mDC: myeloid dendritic cells; fDC: follicular dendritic cells; BCR: B-cell receptor; BTK: Bruton’s tyrosine kinase; BAFF: B cell activating factor; APRIL: a proliferation inducing ligand; APC: antigen presenting cells.

Ofatumumab is a mAb IgG1 anti-CD20 approved for chronic lymphocytic leukaemia. Experience of its use in SLE is restricted to a small number of cases. For example, an SLE patient whose previous flares had responded to rituximab, but became allergic to it, received three infusions of ofatumumab and achieved an SLEDAI decrease from 15 to 2, a reduction of anti-dsDNA antibodies levels >90% and C3 normalization [3]. An SLE patient with auto-immune haemolytic anaemia refractory to rituximab, achieved B-cell depletion after ofatumumab, with remission of autoimmune haemolytic anaemia and a SLEDAI of 0 [4]. Four patients with LN achieved proteinuria and anti-dsDNA reduction after ofatumumab [5]. Formal clinical trials in SLE are awaited.

Obinutuzumab, a glycol-engineered mAb anti-CD20, is being used in the treatment of non-Hodgkin’s lymphoma. An in vitro study comparing rituximab to obinutuzumab in SLE demonstrated the latter to be a more efficient B-cell depletor [6]. A 52-week, phase II trial studying safety and efficacy in LN is currently recruiting (NCT02550652). Its primary outcome is complete renal response.

**B-cell intracellular signalling blockade—Bruton’s tyrosine kinase**

Bruton’s tyrosine kinase (BTK) is a component of B-cell receptor signalling, involved in regulating cell proliferation and survival. Its blockade results in B-cell apoptosis. B-cells overexpressing BTK in mice led to anti-dsDNA antibody production and SLE-resembling organ involvement. Many inhibitors of BTK are in development, including ibrutinib and GDC-0853.

Ibrutinib is a tyrosine kinase selective and irreversible inhibitor. It binds to BTK causing B-cell apoptosis. Preclinical trials showed ibrutinib reduced levels of autoantibodies (anti-nucleosome, anti-histone and anti-ssDNA but not anti-dsDNA) and renal disease [7]. However, no current clinical trial is ongoing in SLE.
GDC-0853 is another BTK inhibitor [8]. A phase II trial in SLE is ongoing (NCT02908100), to evaluate the safety and efficacy in patients with moderate-to-severely active SLE.

**T cell co-stimulation blockade**

B-cell immune stimulation follows interaction with T cells and antigen-presenting cells via co-stimulatory signals, notably CD40/40L, CD28, cytotoxic T-lymphocyte antigen 4, and CD80/CD86.

Rigerimod is a 21-mer linear peptide derived from the small nuclear RNP U1-70 K, whose mechanism of action seems to be due to chaperone-mediated autophagy [9]. By reducing the stability of MHC molecules that present antigens to T cells, it blocks antigen presentation to auto-reactive T cells, which in turn blocks B-cells maturation.

A phase II trial involved 20 patients with moderately active SLE who received three s.c. injections. Significant improvement in the SLEDAI score was reported with the 200 μg dose [10]. A phase Ib/II trial showed a significant reduction of disease activity [11]. One hundred and forty-nine patients were randomized to receive rigerimod or a placebo every 2 or 4 weeks. Patients with SLEDAI-2K ≥ 6 who received rigerimod 200 μg every 4 weeks achieved a statistically higher Systemic Lupus Erythematosus Responder Index (SRI)-4 response at week 12 (67.6 vs 41.5%, P < 0.025) and week 24 (84.2 vs 45.8%, P < 0.025). A phase III trial is underway, whose primary outcome is SLEDAI-2K reduction ≥ 4 (NCT02504645).

CD40 ligand (CD40L) is a protein expressed on activated T cells and a member of the TNF family. Its binding to CD40 on antigen-presenting cells and B cells induces co-stimulation and promotes B-cell maturation. Anti-CD40L mAbs block co-stimulation in experimental models. A phase II trial in 28 patients with proliferative LN showed significant reduction in circulating levels of anti-dsDNA antibodies and increased C3 levels, but was associated with thromboembolic events [12]. Another phase II trial of a different anti-CD40L mAb had no major adverse events (AE), however, efficacy was not proven [13]. The thromboembolic events were evidently caused by the functional Fc region of anti-CD40L, which triggers platelet aggregation by interacting with platelet FcγRIIA receptor. In dapirolizumab the Fc portion has been changed to a high molecular polyethylene glycol without loss of efficacy [14]. A 32-week, phase IB trial showed safety and tolerability of intravenous dapirolizumab in SLE patients. Clinical response was evident by both SRI and BILAG-based Combined Lupus Assessment (BILAC) assessments [15]. A 24-week phase II trial, followed by observational period to evaluate efficacy and safety on moderately to severely active SLE is recruiting (NCT02804763). The primary outcome is the BILAC response rate at 24 weeks.

**Interferon blockade**

IFNs are a family of glycoproteins that consist of type I IFN (IFN-α) (including 12 isoforms of IFNα and one of IFNβ) and type II IFN (includes only IFN-γ). IFN-β binds to the type I IFN receptor (IFNR), IFN-γ binds to another receptor. IFN activates multiple signalling pathways, especially Janus kinase. IFN dysregulated activity and signalling is associated with autoimmune disease development. Rarely, when IFN-α has been used, for example, in hepatitis C and cryoglobulinaemic vasculitis, autoimmune conditions, including SLE, have been reported to develop [16, 17]. IFN-I levels are higher in SLE and recent studies have shown a link between IFN-I levels and disease activity.

Rontalizumab is a humanized IgG1 mAb against IFN-α. A phase I trial proved safe but showed no clinical benefit in those with a high IFN signature [18]. A phase II trial evaluated efficacy and safety of rontalizumab in 159 patients with moderate to severe SLE. Patients were randomized to receive rontalizumab 750 mg or placebo every 4 weeks plus standard of care (SOC) (part 1) and subsequently, 300 mg rontalizumab or placebo every 2 weeks (part 2). The results did not confirm rontalizumab’s general superiority, however paradoxically, in the low IFN signature group SRI response rates were superior in 31% (P = 0.0285) and the SELENA-SLEDAI flare index rate was reduced [19]. However, no further trial is ongoing.

Sifalimumab is a fully human IgG1x mAb that binds to most subtypes of IFN-α and neutralizes it. Two phase I trials showed safety and IFN signature reduction in a dose-dependent manner. A 52-week phase Ib trial followed by a 22-week safety follow-up, enrolled 431 patients randomized to receive placebo or sifalimumab (200, 600 or 1200 mg) every 28 days in addition to SOC. In all sifalimumab groups, the response rates were significantly higher than in the placebo group, however, only the group with the high IFN signature patients achieved significant improvement in SRI-4. Cutaaneous Lupus Erythematosus Disease area and Severity Index (CLASI) as well as joint counts showed significant improvement. No differences in lowering anti-dsDNA antibodies or normalizing C3/C4 levels were observed. Herpes zoster was the principal AE as expected by IFN suppression [20]. Currently no phase III trial is ongoing.

Unlike the other IFN blockers, directed against IFN, anifrolumab is a fully human IgG1κ mAb that blocks subunit 1 of the IFNRI and consequently both IFN-α and IFN-β. A phase I trial showed safety and sustained IFN signature reduction in SSc patients. In a 52-week phase IIb lupus trial, 305 patients were randomized to receive placebo, anifrolumab 300 mg or 1000 mg every 4 weeks until week 48 as well as SOC [21]. Active LN or neuropsychiatric SLE were excluded. The primary efficacy end point was a combination of the SR-4 at weeks 24 and 52 with a sustained reduction in oral corticosteroids from weeks 12 to 24. At both weeks 24 and 52, the response was achieved in a significantly higher number of patients receiving both dosages of anifrolumab (300 mg, P = 0.014 and 1000 mg, P = 0.063). When evaluating the sub-groups by IFN signature levels, those with high levels of IFN achieved significantly better results compared with placebo at both 24 and 52 weeks. Significant
### TABLE 1 Biologics used in SLE, mechanism of action, targeted receptors and main trials

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Immunologic action</th>
<th>Evidence to date in SLE</th>
<th>Number of patients</th>
<th>Inclusion criteria</th>
<th>Primary outcome</th>
<th>Therapeutic regime</th>
<th>Results</th>
<th>Future trials in SLE</th>
<th>Inclusion criteria</th>
<th>Primary outcome</th>
<th>Therapeutic regime</th>
<th>Prospects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofatumumab</td>
<td>B-cell depletion</td>
<td>Case reports [3-5]</td>
<td>1, 1 and a series of four patients</td>
<td>-</td>
<td>-</td>
<td>Variable</td>
<td>Reduction on disease activity Anti-dsDNA- A reduction and C3 normalization</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Promising, needs clinical studies</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>B-cell depletion</td>
<td>Pre-clinical [6]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>B-cell depletion 2-fold the rituximab</td>
<td>Phase II ongoing on LN</td>
<td>Class III or IV LN</td>
<td>Complete Renal Response at week 52</td>
<td>1000 mg on days 1, 15, 168 and 182 plus MMF</td>
<td>Promising, awaiting clinical results</td>
<td></td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>BTK inhibition</td>
<td>Pre-clinical [7]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>BTK inhibition on mature B-cells</td>
<td>Phase II ongoing</td>
<td>Moderate to severe SLE</td>
<td>SRI-4 response</td>
<td>Low and high dose daily vs placebo</td>
<td>Promising, awaits results</td>
<td></td>
</tr>
<tr>
<td>GDC-0853</td>
<td>BTK inhibition</td>
<td>Pre-clinical and phase I [8]</td>
<td>111</td>
<td>ITT SLEDAI &gt; 6 No BILAG A</td>
<td>SRI-4</td>
<td>200 μg every 2 or 4 weeks</td>
<td>Improvement in subpopulation SLEDAI &gt; 6. Best results 200 mg every 4 weeks and BICLA response across several endpoints</td>
<td>Phase III ongoing</td>
<td>SLEDAI-2K &gt; 6 points</td>
<td>SRI-4 response</td>
<td>200 mcg every 4 weeks</td>
<td>Very promising, awaits results</td>
</tr>
<tr>
<td>Riderimod</td>
<td>T-cell blockade</td>
<td>Phase Ib [10, 11]</td>
<td>149</td>
<td>LLN</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Phase II ongoing</td>
<td>Moderate to severe disease activity</td>
<td>BICLA response rate at week 24</td>
<td>Three different doses vs placebo</td>
<td>Promising, awaits results</td>
</tr>
<tr>
<td>Dapirolizumab</td>
<td>T-cell co-stimulation blockade</td>
<td>Phase Ib [15]</td>
<td>24</td>
<td>SELENA-SLEDAI&gt;4</td>
<td>SRI-4 and BICLA</td>
<td>First dose 30 mg/kg then five doses of 15 mg/kg every 2 weeks</td>
<td>SRI-4 and BICLA response across several endpoints</td>
<td>Phase II ongoing</td>
<td>SRI-4 response in high IFN signature group</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rontalizumab</td>
<td>IFNα blocker</td>
<td>Phase II [18, 19]</td>
<td>159</td>
<td>Moderate to severe disease activity</td>
<td>BILAG</td>
<td>750 μg every 4 weeks (part 1), 300 μg every 2 weeks (part 2)</td>
<td>No general superiority; in low IFN signature it had significant superiority</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Dubious results</td>
</tr>
<tr>
<td>Sifalimumab</td>
<td>IFNα blocker</td>
<td>Phase Ib [20]</td>
<td>431</td>
<td>SLEDAI-2K &gt; 6</td>
<td>SRI-4</td>
<td>200, 600, or 1200 μg every 28 days</td>
<td>Better SRI-4 response in high IFN signature group</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Promising, awaits results</td>
</tr>
<tr>
<td>Anifrolumab</td>
<td>IFNα blocker</td>
<td>Phase Ib [21]</td>
<td>305</td>
<td>SLEDAI-2K &gt; 6</td>
<td>Composite of SRI-4 and corticosteroids reduction</td>
<td>300 or 1000 μg every 4 weeks</td>
<td>Better SRI-4 response in high IFN signature group</td>
<td>Several phase III including LN and skin lesions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Very promising, awaits results</td>
</tr>
<tr>
<td>IFN-kinoid</td>
<td>Induction of anti-IFNα antibodies</td>
<td>Phase II [22]</td>
<td>28</td>
<td>Mild-to-moderate</td>
<td>-</td>
<td>30, 60, 120, or 240 μg</td>
<td>Dose-related response anti-IFNα Higher C3 level</td>
<td>Phase II trial ongoing</td>
<td>SLEDAI-2K &gt; 6</td>
<td>BICLA response at week 36</td>
<td>Promising, awaits results</td>
<td></td>
</tr>
<tr>
<td>SM101</td>
<td>Autoimmune complexes blockade</td>
<td>Phase Ia [23]</td>
<td>51</td>
<td>SELENA-SLEDAI &gt; 6 LN was included</td>
<td>Safety, SRI-4 and BILAG</td>
<td>6 and 12 mg/kg every week</td>
<td>Better SRI-4 response</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Promising, needs clinical studies</td>
</tr>
<tr>
<td>SM201</td>
<td>Autoimmune complexes blockade</td>
<td>Pre-clinical [24]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>B-cell inhibition</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Very early to know</td>
<td></td>
</tr>
</tbody>
</table>

APC: antigen presenting cells; BICLA: BILAG-based Combined Lupus Assessment; BTK: Bruton’s tyrosine kinase; ITT: intention-to-treat; SRI: Systemic Lupus Erythematosus Responder Index.
improvement was also achieved using BICLA, BILAG 2004; CLASI; joint counts and other variables. Influenza and herpes zoster infections were the most frequent AE. Further studies are ongoing in active SLE patients, including in LN (NCT02547922).

IFN-α-kinoid (IFN-K) is another option in blocking IFN-α. IFN-K is a vaccine composed of IFN-α2b coupled to a carrier protein. It acts by inducing antibody production against all IFN-α subtypes. A phase II/I trial of 28 patients with mild-to-moderate SLE showed a dose-related anti-IFNα response and improvement of C3 levels [22]. A phase II trial is ongoing to elicit IFN signature reduction and efficacy in SLE (NCT02665364).

### Blocking immune complexes

Fcγ receptors (FcγR) are transmembrane proteins that recognize the Fc region of IgG. The binding of immune complexes (ICs) and FcγR initiates intracellular signalling, which results in an autoimmune response. Most of the FcγR molecules act as activating receptors and only FcγRIIb is an inhibitory receptor. Both types of receptors are expressed on the same cells. Negative signalling by FcγRIIb is mainly important for the regulation of activated B cells. SLE patients have a lower expression of FcγRIIb. SM101 is an extracellular version of the human FcγRIIb. It binds to IC in SLE and blocks the Fcγ-activated signal. FcγRIIb was chosen as a therapeutic target because of its limited human polymorphism and lack of immunogenicity.

In a 24-week phase IIa trial, 51 SLE patients were randomized to receive SM101 or placebo weekly for 4 weeks. The primary outcome was safety and the secondary outcomes included SLEDAI, BILAG, physician global assessment, global response and renal parameters. No serious AE were reported. The SRI-4 response was twice as high in the SM101 group and in LN results was even better [23]. The results seem promising but phase III trials are needed.

Rather than binding to IC, binding to the receptor itself can produce an inhibitory response. SM201 is an anti-FcγRIIb mAb, it binds to FcγRIIb but allows the binding between IC and the FcγRIIb. A pre-clinical study showed that SM201 had a synergic action with IC resulting in a better inhibition of B cells [24]. It also seems to be restricted to activated B cells, allowing a functional memory response. Clinical trials are needed to understand if it’s a valid therapeutic.

A resume of ongoing trials relevant to the approaches discussed in this review are shown in Table 1.

### Conclusions

Biologic treatment of lupus has seen many false dawns. The relative successes of belimumab, rituximab, and atacicept (not discussed here) have been counterbalanced by the failures of many others including abatacept, tabalumab, blisibimod, and epratuzumab. But a number of new approaches, including fully humanized anti-CD20, PEGylated anti-CD40L, IFN-α inhibitors and rigerimod, offer new hope that before too long we will have a range of biologic options to offer our SLE patients that matches the choices we have for our RA and PSA patients.

Other approaches, not discussed here, such as blocking the Janus kinase/signal transducers and activators of transcription-pathway, IL-6 and nuclear factor kappa-light-chain-enhancer of activated B cells might also prove of value.

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### References


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